



## **Proposed Registration of Enlist Duo™ Herbicide**

Approved by: \_\_\_\_\_

Lois Rossi, Director  
Registration Division

Date: \_\_\_\_\_

## **Proposed Registration of Enlist Duo™ Herbicide**

### **Regulatory Rationale**

The Agency is proposing to grant a registration for Enlist Duo™, a herbicide containing the active ingredients 2,4-dichlorophenoxyacetic acid (2,4-D) choline salt and glyphosate dimethylammonium salt (glyphosate). Dow AgroSciences (DAS) submitted an application for registration to the Environmental Protection Agency (EPA or the Agency) for this registration, which proposes use on corn and soybean crops that are genetically engineered to be tolerant to 2,4-D and glyphosate (GE crops). DAS has requested that its Enlist™ GE herbicide tolerant crops be deregulated under the Plant Protection Act. The United States Department of Agriculture (USDA) is currently reviewing this request. EPA intends to wait until USDA's review is complete before making a final decision on the Enlist Duo™ application for registration.

2,4-D is a longstanding active ingredient that is used through a variety of salt and ester formulations and registered for a variety of food and feed uses, including corn and soybeans. The proposed use would expand the current timing of applications of 2,4-D on corn and soybeans, thereby enhancing the flexibility in weed control. 2,4-D is currently registered for over-the-top applications to corn up to 8 inches tall and only pre-plant applications to soybeans. The pending application would allow over-the-top applications of 2,4-D choline salt formulation to GE corn up to 48 inches tall and over-the-top applications to GE soybeans.

Although the use on GE crops is a new use pattern for the 2,4 D component of this product, it is not a new use for glyphosate containing products. All uses for this proposed product are already registered on other glyphosate products and are currently in use on GE corn and soybeans for the same use pattern. Since no new use pattern and no new exposures for glyphosate are being considered with this registration action, no new assessment is needed for glyphosate. However, as described above, the expanded timing of applications does change the current use pattern for the choline salt of 2,4-D. Therefore, this document is intended to discuss the results of the Agency's findings specifically to the assessment of the choline salt of 2,4-D on GE corn and soybeans.

### **I. Chemical Information**

**Chemical Name:** Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, 2-(2,4-dichlorophenoxy)acetic acid hydroxide (1:1:1)

**EPA PC Code:** 051505

**Chemical Abstracts Service (CAS) Number:** 1048373-72-3

**Mode of Action:** 2,4-D is an herbicide in the phenoxyacetic acid family that is used postemergence for selective control of broadleaf weeds. 2,4-D, a synthetic auxin herbicide, causes disruption of plant hormone responses.

**Registrant:** Dow AgroSciences LLC

**Proposed Product:** GF-2726 (Enlist Duo™) – EPA File Symbol 62719-AUO, an end-use product containing 24.4% 2,4-D choline salt and 22.1% Glyphosate, to be used on Enlist™ AAD-1 Corn (Trait Code: DAS-40278-9) and Enlist™ AAD-12 Soybean (Trait Code: DAS-68416-4).

## **II. Human Health Risk**

A summary of the human health effects and risk of 2,4-D choline salt as assessed in the EPA document entitled, *2,4-D. Human Health Risk Assessment for a Proposed Use of 2,4-D Choline on Herbicide-Tolerant Corn and Soybean*, is provided below.

### **A. Summary of Toxicological Effects**

The toxicology database on 2,4-D is complete and sufficient for assessing the toxicity and characterizing the hazard of all formulations of 2,4-D, including the choline salt. Data on other forms of 2,4-D were also used to assess the choline formulation.

2,4-D has been classified as having low acute toxicity via the oral, dermal, and inhalation routes of exposure (Toxicity Category III). It is not a dermal irritant (Toxicity Category IV) or dermal sensitizer but it is a severe eye irritant (Toxicity Category I).

The toxicity profile of the active ingredient 2,4-D shows that the principal toxic effects are changes in the kidney, thyroid, liver, adrenal, eye, and ovaries/testes in the rat following exposure to 2,4-D *via* the oral route at dose levels above the threshold of saturation of renal clearance. No systemic toxicity was observed in rabbits following repeated exposure *via* the dermal route at dose levels up to the limit dose. Neurotoxicity was observed in the acute neurotoxicity study in rats at the high dose. In an extended one-generation reproductive toxicity study in rats, reproductive toxicity, developmental neurotoxicity, and immunotoxicity were not observed. The thyroid effects observed at dose levels up to/approaching renal saturation were considered treatment-related, although not adverse. Maternal and developmental toxicity were observed at high dose levels exceeding the threshold of saturation of renal clearance. There are no residual uncertainties for pre- and/or postnatal toxicity.

2,4-D is classified as “not classifiable as to human carcinogenicity,” based upon bioassays in rats and mice that showed no statistically significant tumor response in either species. The Agency determined, based on several reviews of epidemiological studies, in addition to the animal studies, that the existing data did not support a conclusion that links human cancer to 2,4-D exposure.

### **B. Toxicological End Points and Doses Used in the Human Health Risk Assessment**

Once a pesticide’s toxicological profile is determined, EPA identifies toxicological Points of Departure (POD) and Levels of Concern (LOC) to use in evaluating the risk posed by human exposure to the pesticide. For hazards that have a threshold below which there is no appreciable risk, the toxicological POD is used as the basis for derivation of reference values for risk

assessment. PODs are developed based on a careful analysis of the doses in each toxicological study to determine the dose at which no adverse effects are observed (the NOAEL; No Observed Adverse Effect Level) and the lowest dose at which adverse effects of concern are identified (the LOAEL; Lowest Observed Adverse Effect Level). Uncertainty/safety factors are used in conjunction with the POD to calculate a safe exposure level - generally referred to as a Population-adjusted Dose (PAD) or a Reference Dose (RfD) - and a safe Margin of Exposure (MOE). For non-threshold risks, EPA assumes that any amount of exposure will lead to some degree of risk. Thus, EPA estimates risk in terms of the probability of an occurrence of the adverse effect expected in a lifetime. For more information on the general principles EPA uses in risk characterization and a complete description of the risk assessment process, see <http://www.epa.gov/pesticides/factsheets/riskassess.htm>.

## **1. Acute Dietary**

### **a. General Population (Including Infants and Children)**

An acute dietary endpoint for the general population, including infants and children, was selected from the acute neurotoxicity study in rats with a NOAEL of 67 mg/kg. At the study LOAEL of 225 mg/kg, an increased incidence of incoordination and slight gait abnormalities (forepaw flexing or knuckling) and decreased motor activity were observed. A 100X uncertainty factor was applied to account for inter- and intra-species variability. As discussed in section C below, the Food Quality and Protection Act (FQPA) safety factor was reduced to 1X resulting in an acute Population Adjusted Dose (aPAD) of 0.67 mg/kg/day.

### **b. Females of Child-Bearing Age (13-49 years old)**

An acute dietary endpoint for females 13+ was selected from the developmental toxicity study in rats with a NOAEL of 25 mg/kg/day. At the study LOAEL of 75 mg/kg/day, fetal skeletal malformations (14<sup>th</sup> rudimentary ribs) were observed. A 100X uncertainty factor was applied to account for inter- and intra-species variability and the FQPA safety factor was reduced to 1X resulting in an acute Population Adjusted Dose aPAD of 0.25 mg/kg/day.

## **2. Chronic Dietary**

The chronic dietary endpoint was selected from the extended one-generation reproduction toxicity study in rats with a NOAEL of 21 mg/kg/day. At the study LOAEL of 55.6 mg/kg/day for males and 46.7 mg/kg/day for females, kidney toxicity, manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules, was observed and decreased body weight in pups was observed throughout lactation. A 100X uncertainty factor was applied to account for inter- and intra-species variability and the FQPA safety factor was reduced to 1X resulting in a chronic Population Adjusted Dose (cPAD) of 0.21 mg/kg/day.

## **3. Incidental Oral, Short and Intermediate Term**

Short-term and intermediate-term incidental oral endpoints for risk assessment were selected from the extended one-generation reproduction toxicity study in rats with a NOAEL of 21 mg/kg/day. At the study LOAEL of 55.6 mg/kg/day for males and 46.7 mg/kg/day for females, kidney toxicity, manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules, was observed and decreased body weight in pups was observed throughout lactation. A 100X uncertainty factor was applied to account for inter- and intra-species variability and the FQPA safety factor was reduced to 1X resulting in a target MOE of 100 for non-dietary risk assessment.

#### **4. Inhalation, Short and Intermediate Term**

Short-term and intermediate-term inhalation endpoints for risk assessment were selected from the route-specific 28-day inhalation toxicity study in rats with a LOAEL of 0.05 mg/L/day. A NOAEL for portal-of-entry effects was not determined. At the study LOAEL of 0.05 mg/L/day, squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx, which was not totally resolved following a 4-week recovery period, were observed. Human Equivalent Concentrations (HEC)/Human Equivalent Doses (HED) for residential and occupational scenarios were calculated. A 3X uncertainty factor was applied to account for inter-species variability (to account for the pharmacodynamic differences), a 10X uncertainty factor was applied to account for intra-species variability, and a 10X uncertainty factor was applied to account for the lack of a NOAEL. Although there was no assessment of the thyroid in the inhalation study, the rat extended one-generation reproduction toxicity (oral) study performed an assessment of the thyroid for several age groups at dose levels up to/approaching renal saturation. The changes in thyroid hormones observed, along with thyroid histopathological findings, were considered treatment related, although not adverse. The lack of an assessment of the thyroid in the inhalation study is considered inconsequential because the portal of entry endpoint is protective of potential thyroid effects expected to occur at higher concentrations; *i.e.*, at doses that exceed the level of renal clearance. Portal-of-entry effects were observed at all dose levels, and an additional 10X uncertainty factor is applied to the LOAEL to obtain an extrapolated NOAEL used for the inhalation risk assessments. The use pattern indicates that dose levels required to exceed the renal clearance mechanism would not be attained following human inhalation exposure.

#### **5. Dermal (All Durations)**

No quantification of dermal risk is required. Although the dermal toxicity study did not evaluate developmental endpoints, the following were noted:

- a. There was no dermal or systemic toxicity observed following repeated dermal applications to rabbits at the Limit Dose (1000 mg/kg/day).
- b. There was no quantitative susceptibility observed in the developmental or reproductive toxicity studies.
- c. The use of a 10% human dermal absorption factor (DAF) with the oral developmental

LOAEL of 90 mg/kg/day established in the rabbit developmental toxicity study yields a dermal equivalent dose (DED) of 900 mg/kg/day, which is numerically similar to the high-end dermal NOAEL (1000 mg/kg/day) in the dermal rabbit study.

- d. The use of the 10% human DAF with the oral developmental LOAEL of 75 mg/kg/day established in the rat developmental study yields a DED of 750 mg/kg/day.
- e. The developmental findings in the rat and rabbit occurred at oral dose levels exceeding renal clearance, and clear NOAELs were obtained (dermal equivalent doses of 250 and 300 mg/kg/day).
- f. Although there was no assessment of the thyroid in the dermal study, the rat extended one-generation reproduction toxicity (oral) study performed an assessment of the thyroid for several age groups at dose levels up to/approaching renal saturation. The changes in thyroid hormones ( $\downarrow$  T<sub>3</sub> and T<sub>4</sub> with  $\uparrow$  TSH levels) observed, along with thyroid histopathological findings, were considered treatment-related, and not adverse (NOAEL for thyroid effects is  $\approx$ 40 mg/kg/day; DED of 400 mg/kg/day).
- g. The use pattern indicates that dose levels required to exceed the renal clearance mechanism would not be attained following human dermal exposure.

## 6. Cancer

The Cancer Peer Review Committee (CPRC; TXR No. 0050017, dated January 29, 1997) classified 2,4-D as “not classifiable as to human carcinogenicity,” based upon bioassays in rats and mice that showed no statistically significant tumor response in either species. EPA determined, based on several reviews of epidemiological studies, in addition to the animal studies, that the existing data did not support a conclusion that links human cancer to 2,4-D exposure.

## C. FQPA Safety Factor

EPA determined that the 10X FQPA Safety Factor (for the protection of infants and children mentioned above) could be reduced to 1X for the following reasons:

The toxicity database is complete and adequate to assess safety for infants and children. There is evidence of increased susceptibility in the rat developmental toxicity study and in the rat two-generation reproduction study; however, these studies have clearly defined NOAELs/LOAELs, and the points of departure used in the risk assessment are below where these findings occur and are protective. There are acute and subchronic neurotoxicity studies, a developmental neurotoxicity study, a detailed evaluation of thyroid function across life stages, and a developmental immunotoxicity study on 2,4-D. Therefore, the Agency has a complete database addressing potential hazard to infants and children. The exposure assessment will not underestimate children’s exposure to 2,4-D. Further details may be found in the following sections:

## 1. Completeness of the Toxicology Database

The toxicology database for 2,4-D is complete. Acceptable rat and rabbit developmental toxicity studies, a rat two-generation reproduction study, an extended one-generation rat reproduction toxicity study (F1 offspring evaluated for potential effects on the nervous system, immune system, reproductive and endocrine systems, thyroid function, and other systemic toxicity parameters), and acute, subchronic, and developmental neurotoxicity studies in rats are available.

## 2. Evidence of Neurotoxicity

Evidence of neurotoxicity was observed in the acute neurotoxicity study in rats, as evidenced by an increase in the incidence of incoordination and slight gait abnormalities (forepaw flexing or knuckling) during the Functional Observation Battery (FOB) assessment at the high dose in both sexes. In the subchronic neurotoxicity study, relative forelimb grip strength was significantly increased in rats of both sexes at the high-dose level, although there was no treatment-related change in absolute grip strength. Clinical signs of neurotoxicity (decreased motor activity, ataxia, loss of righting reflex, extremities cold to the touch) were observed in maternal rabbits in the developmental toxicity study. Developmental neurotoxicity was not observed in the developmental neurotoxicity study in rats. Neuropathological effects were not observed in any study.

## 3. Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is evidence of increased susceptibility following *in utero* exposure to 2,4-D in the rat developmental toxicity study and following *in utero* and/or pre-/post-natal exposure in the rat two-generation reproduction study. There is no evidence of increased susceptibility following *in utero* exposure to 2,4-D in the rabbit developmental toxicity study or following *in utero* and/or pre-/post-natal exposure in the rat extended one-generation reproduction toxicity study.

2,4-D has been evaluated for potential developmental effects in the rat and rabbit. Maternal toxicity included decreased body weight gains in the rat study at the same dose level where developmental effects (occurrence of skeletal malformations) were observed. Maternal toxicity in the rabbit included decreased body weight gain, clinical signs of toxicity (decreased motor activity, ataxia, loss of righting reflex, extremities cold to the touch), and abortions, the latter being indicative of potential developmental toxicity. Decreased maternal body weight gains were observed in the rat two-generation reproduction study at a dose that exceeded renal saturation and resulted in reduced viability of the F1 pups. There are clearly established NOAELs and LOAELs for the population of concern, there are no data gaps in the toxicology database, and the PODs are protective of susceptibility.

## 4. Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary exposure estimates are unrefined and reflect primarily tolerance-level residue in food, 100% crop treated, and upper-bound drinking water estimates based on modeling. Additionally, non-occupational exposure estimates were determined using the Residential Standard Operating Procedures which utilize a

combination of central tendency and high end inputs designed to result in protective exposure estimates which will not underestimate residential exposures.

#### **D. Cumulative Effects**

2,4-D is an herbicide in the phenoxyacetic acid family of pesticides. This class also includes MCPA, 2,4-DB, and 2,4-DP. A cumulative risk assessment has not been performed as part of this human health risk assessment because EPA has not made a determination as to which of these compounds, if any, to which humans may be exposed, have a common mechanism of toxicity. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to 2,4-D and any other substances. For the purposes of this action, therefore, EPA has not assumed that 2,4-D has a common mechanism of toxicity with other substances.

For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

#### **E. Dietary (Food + Drinking Water) Risk**

2,4-D is a phenoxyacetic acid herbicide used to control a variety of broadleaf weeds. It is a longstanding active ingredient (ai) registered for a variety of food/feed uses. Permanent tolerances for 2,4-D are established under 40 CFR 180.142 for a wide variety of crops and livestock commodities.

Acute and chronic aggregate (food + dietary drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

##### **1. Acute Dietary Risk**

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., only those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with EPA policy, per capita exposure and risk are reported for analyses.

The resulting acute food plus drinking water risk estimates are not of concern to EPA ( $\leq 100\%$

aPAD) at the 95<sup>th</sup> percentile of the exposure distribution for the general population and all population subgroups. The resulting acute risk estimate for children 1 to 2 years old, the subgroup with the greatest exposure, was 14% of the aPAD at the 95<sup>th</sup> percentile of the exposure. The acute dietary assessment is unrefined; to further refine the 2,4-D dietary exposure and risk estimates, percent crop treated (%CT), anticipated residues, or monitoring data, if available, could be used.

## **2. Chronic Dietary Risk**

For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

The resulting chronic food plus drinking water risk estimates are not of concern to EPA for the general population and all population subgroups. The most highly exposed population was children 1 to 2 years old utilizing 15% of the cPAD. The chronic dietary assessment is unrefined; to further refine the 2,4-D dietary exposure and risk estimates, percent crop treated, anticipated residues, or available monitoring data could be used.

## **F. Residential (Non-Occupational) Exposure/Risk Characterization**

There are registered uses of 2,4-D on turf including golf courses and parks as well as aquatic uses; therefore, residential handler exposure and post-application exposure to treated turf and aquatic sites is possible. There is no hazard *via* the dermal route for 2,4-D, therefore the handler assessment included quantification of risks for only the inhalation route of exposure and the post-application assessment included only the inhalation and incidental oral route of exposure. The residential handler and post-application risk estimates are not of concern for 2,4-D for all scenarios and all routes of exposure.

For non-dietary exposures, EPA uses the term Margin of Exposure (MOE) to refer to the risk associated with the exposure estimate. The MOE is defined as the ratio of the selected toxicological POD, usually the NOAEL, to the estimated human exposure. A target MOE of 300 means that the estimated level of human exposure is 300 times lower than the highest dose that produced no adverse effects in the relevant toxicology study. Risk estimates that are not of concern are indicated by an actual MOE of 300 or greater for residential handler exposure and 100 or greater for post-application exposure.

### **1. Residential Handler Exposure**

Residential handlers may receive short-term dermal and inhalation exposure to 2,4-D when mixing, loading, and applying the pesticide to ornamental turf as well as aquatic uses. Only inhalation risk estimates were quantitatively assessed because there is no hazard via the dermal

route for 2,4-D. The handler inhalation exposure scenarios considered were mixing, loading and applying:

- Liquid/Wettable Powder (WP)/Dry Flowable (DF) to Lawns/Turf with Hose-End Sprayer
- Liquid/WP in Water Soluble Packets (WSP) to Lawns/Turf/Aquatic Sites with manually-pressurized handwand
- Ready-to-Use/WP in WSP to Lawns/Turf with Hose-End Sprayer
- Liquid to Lawns/Turf/Aquatic Sites with Backpack
- Liquid/WP/DF to Lawns/Turf with Manually-pressurized handwand or backpack
- Granule to Lawns/Turf with Push-type spreader, Belly Grinder, Spoon, Shaker Can, Cup or Hand dispersal

The MOEs for the six exposure scenarios range from 460 to 3,400,000. Since there is potential risk concern only when MOEs are less than 300, residential handler exposures are not a concern.

## **2. Post-Application Exposure**

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with 2,4-D. The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Incidental ingestion (i.e., hand-to-mouth, object-to-mouth, soil ingestion exposure) from contact with treated turf (children 1 to < 2 years old only)
- Episodic granular ingestion on treated turf (children 1 to < 2 years old only)
- Incidental ingestion of water during recreational swimming (both adults and children 3 to < 6 years old).

Assessment of post-application exposure to turf treated with liquid formulations is protective of exposure to solid formulations. The lifestages selected for assessment are health protective for the exposures and risk estimates for any other potentially exposed lifestages.

### **a. Residential Post-application Exposure for Turf Use**

Incidental oral risk estimates were quantitatively assessed for residential post-application exposure for turf use. The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) have been considered inter-related as it is likely that they occur interspersed amongst each other over time. Episodic granular ingestion on treated turf was not combined as this exposure would not occur as a result of routine behavior and is considered an episodic event related to poisoning.

The residential post-application risk estimates for turf use have MOEs that range from 490 to 430,000 for all incidental oral scenarios so are not of concern for 2,4-D.

### **b. Residential Post-application Exposure for Aquatic Use**

2,4-D is used for aquatic weed control of surface and submerged weeds. Many treatments are applied to aquatic areas where recreational swimming is not likely to occur but some subsurface treatments are made at recreational lakes. Since this can result in individuals being exposed to 2,4-D residues in water by entering these areas if they have been previously treated, there is a 24-hour swimming restriction. The extent of exposure during recreational swimming is assumed to be short-term in duration. Risk estimates were calculated for post-application incidental oral ingestion while swimming in treated lakes or ponds. Inhalation exposure is expected to be negligible for swimmers; therefore, a post-application inhalation assessment was not conducted. Furthermore, the inhalation assessment for residential handlers is expected to be protective of potential post-application exposure and risk.

The residential post-application risk estimates for aquatic use have MOEs that range from 690 to 5,300 for incidental oral ingestion so are not of concern for 2,4-D.

### **3. Residential Bystander Post-application Inhalation Exposure (Volatilization)**

The potential exposure to bystanders from vapor phase 2,4-D residues emitted from treated fields has been evaluated for the proposed use of 2,4-D choline salt on genetically engineered corn and soybean. The two main factors that bystander exposure depends on are the rate at which these chemicals come off of a treated field which is described as the off-gassing, emission or flux, and how those vapors are dispersed in the air over and around the treated field. Volatilization can occur during the application process or thereafter. It can result from aerosols evaporating during application, while deposited sprays are still drying or after as dried deposited residues volatilize. The volatilization assessment used an analysis after sprays dried.

Flux data was submitted measuring flux rates of 2,4-D ethylhexyl ester (EHE), 2,4-D dimethylamine salt (DMA salt) and 2,4-D choline salt. 2,4-D choline salt was found to have a reduced potential for volatility. For this assessment, the data from the 2,4-D choline salt applications only were used as this action specifically seeks registration for 2,4-D choline salt product use in conjunction with GE soybean and corn with resistance traits.

Volatilization modeling for a single day was completed using Probabilistic Exposure and Risk model for fumigants (PERFUM). There are a variety of factors that potentially affect the emission rates of 2,4-D choline salt and subsequent offsite transport and to the extent possible, these factors were considered. They include field condition (e.g., bare soil, growing, or mature crop canopy), field parameters (e.g., soil type, moisture, etc.), formulation type, meteorological conditions, and application scenario (e.g., rate, method). Flux estimates from all monitored trials, a number of field sizes, and various meteorological data were used with PERFUM to estimate risk based on the 2,4-D choline salt field volatility study data.

The field volatility study suggests that volatilization of 2,4-D choline salt from treated crops does occur and could result in bystander exposure to vapor phase 2,4-D choline salt. However, results of PERFUM modeling indicate that airborne concentrations, even at the edge of the treated fields, are not above our levels of concern.

#### **4. Spray Drift**

Spray drift is always a potential source of exposure to residents nearby to spraying operations. Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (e.g., children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them. Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

Several 2,4-D products have existing labels for use on turf, thus it was considered whether the risk assessment for that use may be considered protective of any type of exposure that would be associated with spray drift. If the maximum application rate on crops adjusted by the amount of drift expected is less than or equal to existing turf application rates, the existing turf assessment is considered protective of spray drift exposure. The proposed maximum single application rate of 2,4-D choline salt on GE corn and soybean is 1 lb ae/acre. This is less than the registered application rate on turf of 1.5 lb ae/acre, which has been previously assessed and which was updated based on the revised Standard Operating Procedures (SOPs) for Residential Exposure Assessment. Thus, even if 100% of the application rate of the choline salt formulation on GE corn and soybean is deposited on an adjacent lawn, calculated risk estimates from drift would not be of concern. This again is because all existing registered uses on lawns have been previously assessed and no risks of concern were identified.

#### **5. Aggregate Risk Assessment**

In accordance with the FQPA, EPA must aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, EPA considers both the route and duration of exposure.

##### **a. Acute Aggregate Risk**

The acute aggregate risk assessment includes only food and water exposure. The acute food plus drinking water risk estimates are not of concern to EPA ( $\leq 100\%$  aPAD) at the 95<sup>th</sup> percentile of the exposure distribution for the general population and all population subgroups.

#### **b. Short-Term Aggregate Risk**

The short-term aggregate risk assessment includes food, water, and residential exposure. The resulting short-term aggregate risks are not of concern to EPA (MOEs > LOC of 100) for adults and children.

#### **c. Intermediate-Term Aggregate Risk**

Intermediate-term residential exposures are not likely because of the intermittent application of 2,4-D by homeowners; therefore, the intermediate-term aggregate risk assessment includes only food and drinking water exposure, and are less than or equivalent to the chronic food plus drinking water exposure. The chronic food plus drinking water risk estimates are not of concern to EPA for the general population and all population subgroups.

#### **d. Long-Term Aggregate Risk**

The chronic (long-term) aggregate risk assessment includes only food and water exposure. The chronic food plus drinking water risk estimates are not of concern to EPA for the general population and all population subgroups.

### **6. Occupational Risk Assessment**

#### **a. Short- and Intermediate-Term Handler Risk**

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used (mixing/loading liquid groundboom application, applying spray by groundboom equipment), occupational handler exposure is expected from the new uses.

Occupational handler risk estimates are not of concern (i.e., MOEs > LOC of 300) for all scenarios for use of 2,4-D choline salt on GE corn and soybean. At baseline personal protective equipment (PPE) (i.e., no respirator), the occupational handler inhalation MOE is 4,900 for mixer/loaders and 3,200 for applicators using groundboom equipment.

#### **b. Short- and Intermediate-Term Post-Application Risk**

EPA uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as reentry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such

things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

#### **i. Dermal Post-application Risk**

There is no potential hazard *via* the dermal route for 2,4-D choline salt; therefore, a quantitative occupational post-application dermal risk assessment was not completed.

#### **ii. Inhalation Post-application Risk**

Based on the EPA's current practices, a quantitative occupational post-application inhalation exposure assessment was not performed for 2,4-D choline salt at this time primarily because of the low acute inhalation toxicity (Toxicity Category III) and vapor pressure ( $1.4 \times 10^{-7}$  mm Hg at 25°C for 2,4-D acid).

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers and showed no risks of concern. Handler exposure resulting from application of pesticides outdoors is anticipated to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios. Furthermore, a quantitative volatilization inhalation exposure assessment was assessed for bystanders and indicates no risk of concern for bystanders.

### **III. Environmental Risk**

A summary of the environmental fate and ecological effects and risks of 2,4-D choline salt as assessed in the Agency document titled, *Ecological Risk Assessment for the Section 3 New Use Registration of 2,4-D Choline Salt on Soybean with DAS 68416-4 (2,4-D Tolerant) and 2,4-D + Glyphosate Tolerant Corn and Field Corn*, is provided below.

#### **A. Environmental Fate**

##### **1. Degradation**

The degradation of 2,4-D occurs via oxidative microbially-mediated mineralization in terrestrial environments, and photodegradation in water. Degradation under aerobic soil conditions is rapid to moderately rapid with half-lives ranging from 1.4 to 12.4 days. In terrestrial field dissipation studies, 2,4-D acid half-lives range from 1.1 days to 42.5 days. There are three major degradates (2,4-DCP, 1,2,4-benzenetriol, and chlorohydroquinone (CHQ)) and three minor degradates (include 4-chlorophenol, 4-CPA and 2,4-DCA) of 2,4-D. Formation of these degradates varies by environmental component (e.g., soil vs. water), and availability of oxygen. Under natural conditions certain degradates may be less likely to occur.

## 2. Mobility

Under most environmental conditions 2,4-D is an anionic acid, hence it is expected to be mobile to moderately mobile. Risk of bioaccumulation is low for 2,4-D given the low value of the log octanol/water partition coefficient ( $\log K_{ow} = 0.18$  at neutral pH). The vapor pressure ( $1.4 \times 10^{-7}$  mm Hg) and Henry's Law Constant ( $8.56 \times 10^{-6}$  atm-m<sup>3</sup>/mol) indicate that 2,4-D acid has a low volatility. Preliminary results from a field volatility study performed with 2,4-D choline salt, 2,4-D ethylhexyl ester (EHE), and 2,4-D dimethylamine salt (DMA salt) indicate that the estimated volatility flux rate of 2,4-D choline salt is lower than the EHE and DMA salt formulations.

## B. Ecological Risk

Ecological risk characterization integrates the results of the exposure and ecotoxicity data to evaluate the likelihood of adverse ecological effects. The means of integrating the results of exposure and ecotoxicity data is called the quotient method. For this method, risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic ( $RQ = \text{Exposure} / \text{Toxicity}$ ). RQs are then compared to EPA's levels of concern (LOCs). The LOCs are criteria used by the agency to indicate potential risk to non-target organisms. The criteria indicate whether a pesticide, when used as directed, has the potential to cause adverse effects to non-target organisms.

The risk quotient method was used to determine if 2,4-D choline salt has the potential to cause adverse effects to non-target organisms based on the proposed new use patterns for 2,4-D choline salt. Birds are considered a surrogate for terrestrial-phase amphibians and reptiles, in the absence of taxa-specific data. Submitted ecotoxicity data for 2,4-D choline salt (algae, freshwater fish, and honeybee) support bridging 2,4-D choline salt to 2,4-D acid ecotoxicity data. Only the most sensitive 2,4-D toxicity value from the broader 2,4-D dataset were used in risk quotient calculations, as needed. The major degradates of 2,4-D were considered, and all except 2,4-DCP were eliminated as likely degradates of concern. 2,4-DCP is a major degradate in certain aquatic environments; therefore, 2,4-D and 2,4-DCP were considered stressors of concern in aquatic environments, and 2,4-D alone was considered in terrestrial environments.

The results of this screening-level risk assessment indicate that risks did not result in RQ's that exceeded the Agency's LOC for freshwater fish, estuarine/marine fish, freshwater invertebrates, estuarine/marine invertebrates, terrestrial insects, or aquatic plants for either acute or chronic exposures. Risks for chronic exposures to birds, reptiles, and land-phase amphibians do not result in RQ's that exceed the Agency's LOC for chronic exposures only.

The screening-level analysis indicates that risks for acute exposures to birds, reptiles, and land-phase amphibians do result in RQ's that exceed the Agency's LOC for acute exposures. Additionally, risks for mammals resulted in RQ's that exceed the Agency's LOC for both acute and chronic exposures. Risks for plants resulted in RQ's that exceed the Agency's LOC for both terrestrial monocots and terrestrial dicots. The following sections discuss the results of the risk quotient analyses for these taxonomic groups with potential risk above the Agency's LOC, characterization of those risks, and describe mitigation measures to reduce these potential risks

of exposure to 2,4-D choline salt.

### 1. Risk to Birds:

The risk quotient analysis indicates that potential risks from the proposed 2,4-D choline salt uses result in RQ's that exceed the Agency's LOC for birds only on an acute basis.

*Acute Risk:* The acute oral toxicity study was conducted with the northern bobwhite quail and resulted in a classification of "moderately toxic" to birds on an acute oral basis. Toxic symptoms prior to death were lethargy, reduced reaction to external stimuli, depression, lower limb weakness, wing droop, prostrate posture, loss of righting reflex, and a ruffled appearance. Sub-lethal effects included a drop in body weight at two of the treatment levels (218.7 and 135 mg ae/kg-bw). There was also a decrease in food consumption at the 218.7 mg ae/kg-bw treatment level during the first 3 days after dosing, but this was compensated for by a 2-3 times higher food consumption rate from days 4 through 14.

Two acute dietary studies were available, classifying 2,4-D choline salt as "practically non-toxic" on an acute dietary basis to birds. No mortalities occurred in either study. The northern bobwhite quail study exhibited a slight decrease in body weight gain at the 3035 and 1706 mg ae/kg-diet treatment levels. The mallard duck study exhibited a decrease in body weight gain and feed consumption, but only at the highest treatment level (3035 mg ae/kg-diet).

In order to make the most conservative risk estimation, acute toxicity risk quotients were based on the oral toxicity study for the northern bobwhite quail. Risk quotients ranged from 0.01 to 4.18.

Risk quotients for birds span a range of 0.01 to 4.18 which are then compared to the Agency's screening level of concern for non-listed species ( $RQ > 0.5$ ). The Agency risk screening assessment employed residue estimates based on reasonable upper bound assumptions and the maximum labeled rate of the pesticide to determine the RQ values. At this high end exposure, residues for a variety of food items combined with a variety of body sizes triggered the screening concern threshold when compared to the most sensitive oral dose toxicity estimate. While concern levels are triggered, further consideration of all lines of evidence does suggest that risks under more usually encountered circumstances may be lower. For example, high end residues compared to toxicity study endpoints using chemical actually incorporated in the animal's diet do not trigger non-endangered species concerns, suggesting that 2,4-D choline consumed in the diet may possibly be less available than assumed using dose-based exposures. Further, more frequently expected residues levels, such as mean or median estimates of exposure would be lower by a factor of two or more, suggesting that residues are often not likely to trigger concerns for many food items. In addition, screening estimates of exposure and risk are maximal at the actual point of application, right on the field. Available information in the Agency risk assessment indicates that the transport of pesticide off field by spray drift decreases with distance, suggesting that exposures to 2,4-D choline salt and attendant risks can be substantially lower for organisms with territories established at distance from the field. With this last line of evidence in mind, a mitigation step has been incorporated into the pesticide label to require a 30 foot spray setback from areas likely to be habitat for

birds in order to further reduce off-site exposure for birds.

## **2. Risk to Mammals:**

The risk quotient analysis indicates that potential risks from the proposed 2,4-D choline salt uses result in RQ's that exceed the Agency's LOC for mammals in both acute and chronic scenarios.

Risk quotients for mammals exceeded the Agency's LOCs for mammals for acute dose-based exposure and chronic dose-based and dietary-based exposure. The chronic dose-based LOC (1.0) was exceeded for all size classes of mammals consuming all food items except for seeds. The chronic dietary-based LOC (1.0) was exceeded for diets of short grass, tall grass, broadleaf plants, and arthropods for mammals.

*Acute Risk:* The acute toxicity of 2,4-D choline salt to mammals was assessed using the oral gavage study conducted on laboratory rat. Based on the LD<sub>50</sub>, 2,4-D choline salt is moderately toxic to mammals on an acute basis. The dose-based acute mammalian risk quotients ranged from <0.01 to 0.57.

The acute LOC (0.5) was exceeded only for small mammals consuming short grass. All other scenarios resulted in RQ's that did not exceed the Agency's LOC. Because this assessment is conducted under screening level assumptions designed to be conservative (i.e., in the treated field, maximum use rates, eating only the single food source that is expected to result in the greatest exposure, high-end environmental exposures), EPA expects that actual risks to these mammals is lower. Any deviation from this worst case scenario would result in lower risk estimates and would be expected to result in RQ's lower than the Agency's LOC.

*Chronic Risk:* The two-generation chronic study with the laboratory rat indicated endpoints in parents and offspring growth to be the most sensitive. Some reproductive effects were also identified. Chronic dose based risk quotients ranged from 0.32 to 50.2. The chronic LOC of 1.0 was exceeded for all size classes of mammals consuming all food items except for seeds. Chronic dietary based risk quotients ranged from 0.36 to 5.78.

As in the case for birds, risk quotients for mammals span an appreciable range of outcomes. The principal focus is on the concern levels for reproduction effects, where RQ values range from <1 to 50, and span the Agency's screening level of concern for non-listed species (RQ $\geq$ 1).

Again, the Agency risk screening assessment employed residue estimates based on reasonable upper bound assumptions and the maximum labeled rate of the pesticide to determine the RQ values. Consideration of more usual residue estimates and other lines of evidence such as food preferences and foraging ranges relative to distance from the site of application can lead to markedly reduced concerns for adverse effects in larger mammals with more varied diets, with larger home ranges with increased potential to be feeding well away from treatment areas.

Consideration of these lines of evidence also produces reduced risk estimates for small herbivorous mammals but do not reduce risk estimates for these organisms to the point that

concern levels are not exceeded. As in the case for birds, the provision of a 30-foot buffer from areas potentially comprising habitat for such mammals is intended to reduce the areas where such risks may occur.

### **3. Risk to Plants:**

For this risk assessment, data from other forms of 2,4-D were used as surrogates for the 2,4-D choline salt and 2,4-D choline salt/glyphosate products. For seedling emergence, onion was the most sensitive monocot and lettuce was the most sensitive dicot. Shoot length was the most sensitive parameter for both species, as well as for four of the other species that were tested (tomato, cucumber, soybean, turnip). Seedling emergence was the most sensitive parameter for one species (cabbage) and other toxicological observations included chlorosis and leaf curl. Onion and lettuce were also the most sensitive species for the vegetative vigor test. The most sensitive parameter for onion was fresh weight. Leaf distortion and necrosis were also observed. The most sensitive parameter for lettuce was dry weight. Chlorosis, necrosis, leaf curl, stem curl, wilt, and adventitious growth were also reported as effects. Overall, the vegetative vigor and seedling emergence studies indicate that 2,4-D choline salt is slightly more toxic to dicots than monocots.

As is expected with herbicides, terrestrial plants are sensitive to 2,4-D residues. All terrestrial plant risk quotients exceeded the LOC (1.0). Risk quotients ranged from 1 to 90.62 for monocots and 12.35 to 1085.11 for dicots. Risk was attributed to both spray drift and runoff from treated fields. Thus, the risk quotient analysis indicates that effects are predicted from the proposed new uses of 2,4-D choline salt to terrestrial plants.

Although the risk quotient analysis indicates there may be risks to terrestrial plants from runoff and spray drift, data conducted on the 2,4-D choline salt formulation proposed for registration demonstrates that the formulation maintains some properties that may reduce spray drift to non-target areas. The registrant submitted additional studies for spray drift analysis, using the AIXR 11004 nozzle and the specific 2,4-D choline salt formulation proposed for registration in this action. The analysis indicates that this 2,4-D choline salt formulation applied through the AIXR 11004 nozzle is protective of non-listed dicots from exposures of 2,4-D choline when an adequate buffer is incorporated between the application equipment and the downwind edge of the treated field. Therefore, to mitigate against potential risks to plants, the product labeling will require the use of a 30 foot buffer zone and specific nozzle specifications, thus reducing the potential exposure of non-target plants to 2,4-D choline salt residues.

### **4. Endangered Species for 2,4-D Choline Salt**

A summary of the endangered species assessment for 2,4-D choline salt as assessed in the EPA document titled, *Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Endangered Species Assessment for Proposed New Uses on Herbicide-Tolerant Corn and Soybean*, is provided below.

In the environmental risk assessment performed for new uses of 2,4-D choline salt on GE corn and soybean, EPA determined that direct concerns were unlikely for aquatic plants (vascular

and non-vascular), freshwater fish (acute and chronic), estuarine/marine fish (acute and chronic), freshwater invertebrates (acute and chronic), estuarine/marine invertebrates (acute and chronic), and terrestrial insects. While direct concerns were found to be unlikely for birds, reptiles and terrestrial phase amphibians for chronic risk, they could not be excluded for acute risk. In addition, potential direct risk concerns could not be excluded for mammals (acute and chronic) and terrestrial plants. Indirect effect risk concerns are possible for any species that has dependencies on species that are directly affected.

Registration of Enlist Duo™ is currently being considered for use in the states of Illinois, Indiana, Iowa, Ohio, South Dakota, and Wisconsin. Based on EPA's LOCATES database and data submitted by DAS, 53 listed species were identified as inside the "action area" (area of concern where use of pesticide may result in exposure to endangered species) associated with the new GE corn and soybean uses within these six states. Additional states may be added to the labeling once an assessment is completed and demonstrates that a no effects determination is appropriate for any such state.

The following criteria are used to make an effects determination:

- For listed individuals inside the action area but not part of an affected taxa nor relying on the affected taxa for services involving food, shelter, biological mediated resources necessary for survival and reproduction, use of a pesticide would be determined to have "no effect."
- For listed individuals outside the action area, use of a pesticide would be determined to have "no effect."
- Listed individuals inside the action area may either fall into the "no effect" or "may effect" categories depending upon their specific biological needs and circumstances of exposure.
- Those that fall under the "may effect" category are found to be either "likely" or "not likely to adversely affect" the listed species.
- A "likely" or "not likely to adversely affect" determination is made using criteria that categorizes the effect as insignificant, highly uncertain, or wholly beneficial.

Spray drift mitigation language on the label is intended to limit off site transport of 2,4-D choline salt in spray drift. Therefore, EPA expects that spray drift will remain confined to the 2,4-D choline treated field and that the action area is limited to this field. Consequently, 49 of the 53 species originally identified as potentially at-risk can be given a "no effect" determination based on the premise that they are not expected to occur on corn and soybean fields.

The 4 remaining listed species that were not ruled out because their range contains areas that include treated fields were considered in more depth to refine the assessment. Species specific biological information and 2,4-D choline salt use patterns were considered. After utilizing processes such as refined modeling incorporating species specific information and migration habits, EPA made a determination of "no effect" for these species.

For more details on these findings, refer to the EPA document titled, *Addendum to 2,4-D Choline Salt Section 3 Risk Assessment: Refined Endangered Species Assessment for Proposed*

### *New Uses on Herbicide-Tolerant Corn and Soybean.*

As noted earlier in this decision, glyphosate is already registered for these uses and did not undergo review as part of the assessment for this pesticide product. However, glyphosate currently is in the registration review process and an ESA analysis will be part of that process.

## **IV. Resistance Management**

The emergence of herbicide resistant weeds is an increasing problem that has become a significant economic issue to growers. This has led to a concern that the use of 2,4-D on GE crops may result in more resistant weeds. In an effort to address this issue going forward, EPA is requiring that DAS develop a stewardship program that will aggressively promote resistance management efforts.

The overall goal of the stewardship plan is to assist and support responsible use of the product. With regard to weed resistance management, the plan mandates that DAS must immediately investigate any claims of non-performance. The initial mechanism users can use for communicating directly with DAS is a toll-free number to get advice on how to resolve any uncontrolled weeds.

Academia, growers, USDA, and other leaders involved with pest management acknowledge the importance of field scouting. For this reason, the Enlist Duo™ label includes a requirement to scout treated fields. Field scouting before application will be essential to determining the weed species present as well as their stage of growth. Scouting 7-21 days after herbicide application will be used to assess the performance of weed control. In the event that a user encounters a non-performance issue, the toll-free number could be used to initiate an intervention against that weed population.

The DAS response to reports of non-performance must be immediate and must ensure that possible incidents of resistance are promptly investigated and resolved. EPA proposes that when a non-performance issue is identified, DAS or its representative will conduct a site visit and evaluate the issue using decision criteria identified by leading weed science experts (Norsworthy, et al.), in order to determine if “likely herbicide resistance” is present. This is distinct from, and more broad than, the term “likely herbicide resistance,” as explained below. For purposes of this decision, a report of non-performance to DAS will be the trigger for a site visit.

Non-performance refers to any cause that results in inadequate weed control after an herbicide application. “Lack of herbicide efficacy” refers to inadequate weed control with various possible causes, including but not limited to: application rate, stage of growth, environmental conditions, herbicide resistance, plugged nozzle, boom shut off, tank dilution, post-application weed flush, unexpected rainfall event, weed misidentification, etc. EPA recognizes that it can be challenging to determine emerging weed resistance at an early stage. Therefore, EPA is selecting criteria that it feels will be helpful to DAS and to users in identifying when instances of “lack of herbicide efficacy” in fact constitute “likely herbicide resistance.” These “likely herbicide

resistance” criteria are: (1) failure to control a weed species normally controlled by the herbicide at the dose applied, especially if control is achieved on adjacent weeds; (2) a spreading patch of uncontrolled plants of a particular weed species; and (3) surviving plants mixed with controlled individuals of the same species (Norsworthy, et al., 2012).

When DAS or its representative applies the Norsworthy, et al., criteria cited above and likely herbicide resistance is identified, then DAS must take immediate action to eradicate likely resistant weeds in the infested area. This may be accomplished by re-treating with an herbicide or using mechanical control methods. If herbicide re-treatment is used to eliminate the likely resistant weed(s), follow-up scouting will be required to confirm that the lack of herbicide efficacy has been resolved. DAS must also notify EPA that likely herbicide resistance has been identified and report this on a monthly basis. In addition, samples of the likely herbicide resistant weeds and/or seeds must be taken, and prior to the next growing season laboratory or greenhouse testing must be initiated in order to determine whether resistance is the reason for the lack of herbicide efficacy. DAS must also work to develop a laboratory diagnostic test to quickly identify herbicide resistance, and report to EPA its progress toward developing such a diagnostic test.

In addition to reporting incidents of likely resistance, on or before October 15 of each year, DAS will submit annual summary reports to EPA. These reports must include a summary of the number of instances of likely and confirmed resistance to Enlist Duo™ by weed species, crop, county and state. They will also summarize the status of laboratory or greenhouse testing for resistance, as well as the status of the development of a laboratory test. The annual reports will also address the disposition of incidents of likely or confirmed resistance reported in previous years.

Users and other stakeholders must be informed of reports of likely and confirmed herbicide resistance to Enlist Duo™, if any. The information will include details of weed species and crop. To accomplish this, EPA expects that DAS will establish a website to facilitate delivery of resistance information.

Several management practices that are designed to help users avoid initial occurrences of weed resistance will appear on the product labeling under the Resistance Management heading of the label. These practices are discussed in Section VII.B.3 of this document.

Refer to Section VII.C below for EPA’s delineation of necessary terms of registration to address the issue of weed resistance.

## **V. Response to Comments**

The Agency received more than 100,000 comments in response to the Notices of Receipt (Docket Numbers: EPA-HQ-OPP-2011-0835 and EPA-HQ-OPP-2012-0306) for the applications to register the use of 2,4-D choline salt on GE 2,4-D and glyphosate tolerant corn and soybeans. Some of the comments were in favor of a decision to register Enlist Duo™, which is expected to provide growers with additional tools to control a broad spectrum of weeds. However, the large

majority of comments expressed concern and requested that the Agency deny the proposed registrations. The EPA welcomes input from the public during the decision process when registering pesticides, and is committed to thoroughly evaluating and mitigating any potential risks from registered pesticides, consistent with applicable statutory standards. Also, EPA strives to document and explain the bases of its regulatory decisions through these and other public documents.

## **A. Human health**

A common concern expressed in the submitted comments was regarding the human health effects of the potential increased use, and therefore exposure of, 2,4-D.

### **1. Agent Orange/Dioxins**

Comments were received that expressed concern regarding the dangers of dioxins, and their association with 2,4-D. The herbicide Agent Orange, which was used by the military during the 1960s, was a mixture of the herbicides 2,4,5-T and 2,4-D. Agent Orange was contaminated with dioxin, or 2,3,7,8-TCDD, a by-product of the manufacturing process at that time. In 1970, the United States Department of Agriculture (USDA) stopped the use of 2,4,5-T on all food crops except rice, and in 1985 EPA terminated all remaining uses in the U.S. The herbicide 2,4-D has been reviewed extensively in past years. Since the 1980s, the manufacturers of 2,4-D have taken steps to decrease the chances that dioxin contaminants will be formed during the production process. In periodically reviewing 2,4-D, EPA has required the manufacturers to provide data on dioxin levels in 2,4-D products to confirm that the products can be used safely. Potential dioxin contamination is no longer a factor in the modern manufacturing processes for 2, 4-D.

### **2. Toxicological Effects**

Several comments were received expressing concern with a variety of potential adverse effects on humans. The comments included concerns with Non-Hodgkin's Lymphoma, carcinogens, Parkinson's disease, epidemiology, and other effects attributed to increased use of 2,4-D. These concerns are discussed below.

#### **a. Non-Hodgkin's Lymphoma**

Regarding the alleged association of exposure to 2, 4-D and non-Hodgkin's lymphoma (NHL), the Agency on numerous occasions has concluded that the data are inadequate to support a link between 2,4-D exposure and cancer of any type (most recent assessment can be found in the Agency's response to NRDC petition, 2012). The Agency will further evaluate research related to 2,4-D under registration review, including any new epidemiology data.

**b. Carcinogens**

The Agency has evaluated on several occasions the issue of human carcinogenicity, based on epidemiological links of 2, 4-D to NHL, as well as mutagenicity potential. EPA has consistently found that these data do not support classification of 2,4-D as a carcinogen.

**c. Parkinson's Disease**

Epidemiological studies in the open literature linking Parkinson's disease with 2,4-D exposure will be addressed during the Registration Review of all 2,4-D formulations, taking into account the fact that 2,4-D use patterns have changed in agriculture since the timeframes where the cited data were generated and possible confounding aspects, such as potential dioxin contamination, which are no longer a factor in the modern manufacturing processes for 2,4-D.

**d. Epidemiology**

The Agency has on several occasions reviewed epidemiology studies asserting a link between cancer and 2,4-D exposure. EPA concluded that the existing data did not support the link. During Registration Review, all new epidemiology information will be considered. During the registration review process, the Agency is also involved in many efforts to refine its risk assessment policies including establishing better methods for considering epidemiological research in the regulatory process; and more active participation with several epidemiological cohorts focused on agriculture and the use of pesticides. The Agency will further evaluate research related to 2,4-D under registration review.

**e. Other**

Commenters expressed concern about a range of other health effects. Prior to approval or registration by EPA, pesticides undergo a battery of scientific studies on a wide range of health effects, including cancer, reproductive effects, neurological effects, and acute and chronic toxic effects, and must demonstrate that the product meets the statutory standard and can be used without unreasonable risks. The Agency also periodically reviews all registered pesticides to make sure that they continue to meet current scientific and regulatory standards. If, at any time, EPA determines that there are urgent risks from exposure to a pesticide that require prompt attention, the Agency can initiate appropriate regulatory action.

EPA has a full and scientifically robust data set on 2,4-D, and has a conservative and protective risk assessment based on NOAEL considerations and protective safety factors. More detail on EPA's assessment of human health risk is in Section II of this document.

**B. Environment**

Another area of concern for many commenters was the risk of adverse environmental impacts from the increased application of 2,4-D.

## **1. Endangered Species**

Comments were received concerning possible effects with respect to endangered species. The Agency has conducted a thorough evaluation of the 2,4-D choline salt component to determine the potential impacts from the proposed action to endangered species and has concluded that no impact to endangered species is expected. A discussion of the Agency's endangered species assessment is included in this document and can be found in Section III of this document.

## **2. Spray Drift/Volatilization**

A portion of commenters expressed concerns of spray drift and volatilization of 2,4-D affecting non-target plants. The Agency understands and has evaluated the risks regarding the potential drift of pesticides to sensitive crops adjacent to treatment areas, and other non-target plants. EPA has examined data confirming that the choline salt of 2,4-D will reduce spray drift and volatility compared to other forms of 2,4-D currently registered. As a result, the use of the choline salt of 2,4-D would result in reduced off-site movement of the herbicide. To ensure there is reduced off-target movement, the proposed regulatory decision pertains only to the use of the same formulation (the choline salt) and specific spray nozzle employed in the registrant's submitted drift studies. In addition, the proposed registration decision requires a 30-foot on-field buffer zone to help minimize spray drift from the intended use area. The proposed label also specifies that Enlist Duo<sup>TM</sup> cannot be applied when the wind speed is over 15 mph, and no aerial application is permitted. With employment of these label restrictions, drift from the treated field is not expected, protecting non-target plant species.

More details on the EPA and DAS' efforts to minimize effects to non-target plant species can be found in Section IV of this document.

## **3. Weed Resistance**

Commenters also expressed concerns that weeds resistant to 2,4-D and glyphosate will be more prevalent as a result of this proposed use. Weed resistance is an increasing problem that has become a significant economic issue to growers. In an effort to prevent new weed resistance from happening, while giving growers another essential tool in their integrated pest management programs, DAS will put into place a stewardship program to promote responsible use of the proposed product in order to minimize the potential for increased levels of weed resistance. This plan is discussed in detail in Section IV of this document.

## **4. Risk to Bees**

The concern of risk to bees was conveyed in the comments. Conservative, screening level risk assessments have determined 2,4-D choline salt to be practically non-toxic to bees. Therefore, the Agency expects that there will be no adverse impacts to bees or other pollinators as a result of the proposed action. Regardless, the Agency is working aggressively to protect bees and other pollinators from the potential effects of pesticides and is engaged in national and international efforts to address those concerns. The Agency works with beekeepers, growers, pesticide manufacturers, the U.S. Department of Agriculture (USDA) and States to apply

technologies to reduce pesticide exposure to bees, advance best management practices, enhance enforcement guidance, and to ensure that real-world pollinator risks are accounted for in our pesticide regulatory decisions.

## **5. Sensitive Non-target Plants**

A portion of commenters expressed concerns of spray drift and volatilization of 2,4-D affecting non-target plants, particularly to growers of sensitive crops, such as vegetables. EPA has examined data confirming that the choline salt of 2,4-D will reduce spray drift and volatility compared to other forms of 2,4-D currently registered. As a result, the use of the choline salt of 2,4-D would result in reduced off-site movement of the herbicide.

Spray drift from the 2,4-D choline salt formulation is also reduced through the use of specific nozzles that produce a coarse droplet size. EPA has re-evaluated the spray drift buffers that would be required to protect the most sensitive taxonomic group, listed dicots. The spray drift buffer distances were calculated using the droplet spectrum for a specific nozzle/formulation combination (AIXR 11004 nozzle and Enlist Duo™ product formulation). The spray drift buffer analysis found drift from the treated field is not expected beyond a 30-foot buffer distance.

To mitigate the risk of off-target movement, the proposed regulatory decision pertains only to the use of the same formulation and specific spray nozzle employed in the registrant's submitted drift studies. In addition, the proposed registration decision requires a 30-foot on-field buffer zone to help minimize spray drift from the intended use area. The proposed label also specifies that Enlist Duo™ cannot be applied when the wind speed is over 15 mph, and no aerial application is permitted.

## **C. Other Concerns**

### **1. Competitive Advantage**

Concerns that the Agency will be competitively favoring DAS by granting the proposed new uses were also communicated. Under the FIFRA pesticide registration process, the Agency reviews only those pesticides and only those uses requested by the requestor / pesticide registrant.

### **2. Glyphosate**

Some comments were received regarding the active ingredient glyphosate. It is acknowledged that the proposed product contains glyphosate as well as 2,4-D choline salt as an active ingredient. However, although the use on GE crops is a new use pattern for the 2,4-D component of this product, it is not a new use for glyphosate. Glyphosate products are currently registered and used for corn and soybeans in the identical manner as specified in this proposed product. EPA affirms that the existing risk assessment for glyphosate fully considers its potential uses and exposures from use on corn and soybean and concludes that its use is protective of the public and meets the standards of FIFRA and FQPA. Because a new

assessment for the application of glyphosate to Enlist™ crops does not require a new human health or environmental risk assessment, comments concerning glyphosate are not being requested in this public comment period. However, glyphosate is currently under registration review, and EPA will invite public comments throughout that process. The most recent information on risks for glyphosate can be found in the Registration Review Docket EPA-HQ-OPP-2009-0361.

## **VI. Benefits**

The need for additional tools to manage resistant weeds has become important as resistance to glyphosate and other herbicides has become a significant economic and pest management issue to growers. The new uses of 2,4-D choline salt could expand options for weed control in corn and soybean and enable control of some resistant biotypes. Current registered uses of non-choline 2,4-D in corn allow for over-the-top broadcast applications only up to 8 inches tall which would be increased to up to 48 inches tall with GE 2,4-D resistant corn. Similarly, the currently registered use of non-choline 2,4-D in soybeans allows pre-plant applications only, however new uses of 2,4-D choline salt would expand uses to include over-the-top broadcast applications to GE soybeans. If registered, the addition of this new tool to the production of soybeans is expected to have a significant impact to broadleaf weed control.

The introduction of a premix formulation combining 2,4-D choline salt and glyphosate to be used on Enlist™ corn and soybeans can provide additional benefits. The use of a premix of 2,4-D choline salt and glyphosate utilizes multiple mechanisms of action and it, if utilized as part of a weed resistance management plan, could delay the development of herbicide resistant weeds. The pairing of two herbicides into a systems approach with a GE crop will allow growers and applicators the opportunity to control many weeds in a way which fulfills the important principle of using multiple mechanisms of action, which the weed science community has been touting for many years.

The use of 2,4-D choline salt and glyphosate on the Enlist™ corn and soybean seed technology would provide efficacious control of broadleaf weeds later in the growing season, resulting in reduced spread and persistence of many broadleaf weeds. When the two herbicides are controlling weeds that are not resistant to either herbicide, this weed control system could prolong the use of glyphosate technology. In addition, this system could maintain the positive effect of reducing the need for tillage, thus preventing unnecessary erosion, in areas where 2,4-D choline salt will control glyphosate resistant broadleaf weeds.

The use of the 2,4-D choline salt offers environmental benefits over the use of traditional forms of 2,4-D as well. Specifically, EPA has determined that the choline salt is less volatile than other forms of 2,4-D. Data also indicates that 2,4-D choline salt has less potential for off-site movement through spray drift than other forms of this herbicide. This would reduce the potential for damage to non-target plants, including vulnerable crops, where 2,4-D choline salt is to be used.

## **VII. Proposed Registration Decision**

Based on these considerations, consistent with the requirements of FIFRA Sec. 3(c)(5), EPA concludes that (i) the Agency has satisfactory data pertaining to the proposed uses of Enlist Duo™ on corn and soybeans; and (ii) approving this application as set forth below will not cause any unreasonable adverse effect on the environment. Accordingly, the Agency proposes to grant this registration with certain terms necessary to ensure that if weed resistance is likely, EPA can act quickly to address the problem.

### **A. Data Requirements**

There are no outstanding data requirements required to support the proposed registration of this action. Although there are data that may be required in connection with registration review activities for 2,4-D, those requirements would be generic to 2,4-D uses and products in general and would be handled in accordance with the registration review process.

### **B. Labeling Requirements**

In order to mitigate risks to non-target plants and animals, label language will be required that is intended to keep the pesticide on the treatment area, thereby reducing the potential for exposure of non-target plants and animals. For example, spray drift management language will be required on the occupational/commercial labeling that advises users of applicator responsibilities and requires specific techniques to reduce the possibility of spray drift. In addition, surface and ground water advisories will be required on all labeling, which may further reduce residues in drinking water and exposure of non-target organisms.

#### **1. Environmental Hazards**

Do not apply directly to water, to areas where surface water is present, or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwaters or rinsate.

#### **2. Worker Protection**

Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. For any requirements specific to your state or tribe, consult the agency responsible for pesticide regulation.

Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 48 hours. PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water, is:

- Coveralls
- Chemical resistant gloves made of any waterproof material

### 3. Resistance Management

#### a. Herbicide Selection:

- Apply full rates of GF-2726 for the most difficult to control weed in the field at the specified time (correct weed size) to minimize weed escapes.
- Rotate the use of this product with non-Group 4 and non-Group 9 herbicides.
- Utilize sequential applications of herbicides with alternative modes of action.
- Avoid using more than two applications of GF-2726 and any other Group 4 or Group 9 herbicide within a single growing season unless mixed with another mode of action herbicide with overlapping weed spectrum.
- Use a broad spectrum soil applied herbicide with other modes of action as a foundation in a weed control program.

#### b. Crop Selection and Cultural Practices:

- Incorporate additional weed control practices whenever possible, such as mechanical cultivation, crop rotation, and weed-free crop seeds, as part of an integrated weed control program.
- Do not allow weed escapes to produce seeds, roots or tubers.
- Thoroughly clean plant residues from equipment before leaving fields suspected to contain resistant weeds.
- Scout fields before application to ensure herbicides and rates will be appropriate for the weed species and weed sizes present.
- Scout fields between 7 and 21 days after application to detect weed escapes or shifts in weed species.
- If resistance is suspected, treat weed escapes with an alternate mode of action or use non-chemical methods to remove escapes.
- User report any incidence of non-performance of this product against a particular weed species to the DAS representative.

### 4. Spray Drift Management

#### a. Droplet Size:

Use AIXR 110-04 spray nozzles with proper tank mix and pressure not to exceed 40 psi to reduce Enlist Duo<sup>TM</sup> Herbicide driftable fines.

#### b. Groundboom Application:

Use the minimum boom height based upon the nozzle manufacturer's directions. Spray drift potential increases as boom height increases. Spray drift can be minimized if nozzle height is not greater than the maximum height specified by the nozzle manufacturer for the nozzle selected.

**c. Wind Speed:**

Do not apply at wind speeds greater than 15 mph.

**d. Temperature and Humidity:**

When making applications in low relative humidity, set up equipment to produce larger droplets to compensate for evaporation. Droplet evaporation is most severe when conditions are both hot and dry.

**e. Temperature Inversions:**

If applying at wind speeds less than 3 mph, the applicator must determine if: a) conditions of temperature inversion exists, or b) stable atmospheric conditions exist at or below nozzle height. Do not make applications into areas of temperature inversions or stable atmospheric conditions.

**f. Application Restrictions**

Do not aerially apply this product.

**5. Protection of Sensitive Areas:**

To ensure the protection of threatened or endangered species, residues of this product from spray drift must be below levels of concern for threatened and endangered species for any area adjacent to the application site that is not excluded as possible habitat for these organisms.

**a. Buffer**

You must maintain a 30-foot downwind buffer from any area that is not:

- Roads, paved or gravel surfaces.
- Planted agricultural fields.
- Agricultural fields that have been prepared for planting.
- Areas covered by the footprint of a building, shade house, green house, silo, feed crib, or other man made structure with walls and or roof.

**b. Wind Direction**

To maintain the required downwind buffer zone:

- Measure wind direction prior to the start of any swath that is within 30 feet of a sensitive area.
- No application swath can be initiated in, or into an area that is within 30 feet of a sensitive area if the wind direction is towards the sensitive area.

## **6. Susceptible Plants:**

Do not apply under circumstances where spray drift may occur to food, forage, or other plantings that might be damaged or crops thereof rendered unfit for sale, use or consumption. Avoid contact of herbicide with foliage, green stems, exposed non-woody roots of crops, desirable plants; including cotton and trees, because severe injury or destruction may result. Small amounts of spray drift that may not be visible may injure susceptible broadleaf plants. Before making an application, please refer to your state's sensitive crop registry (if available) to identify any commercial specialty or certified organic crops that may be located nearby.

Commercially grown tomatoes and other fruiting vegetables (EPA crop group 8), cucurbits (EPA crop group 9), and grapes are particularly sensitive to drift from this product. Do not apply when wind direction favors off-target movement onto these crops.

## **C. Registration Terms**

EPA has determined that certain registration terms are needed to ensure that likely weed resistance as discussed in section IV can be adequately addressed. EPA believes that it is important to address likely weed resistance and not wait until confirmation of resistance has been found. EPA is basing the registration terms on a list of criteria, presented in the peer-reviewed publication, Norsworthy, et al., "Reducing the Risks of Herbicide Resistance: Best Management Practices and Recommendations," *Weed Science* 2012 Special Issue: 31–62 (Norsworthy criteria).

### **1. Stewardship Program**

EPA has determined that the registration must contain a term that requires DAS to have a stewardship program for Enlist Duo™. DAS has begun developing its program which it states is focused on educating and training retailers, farmers and applicators on the appropriate use of the Enlist™ technology. EPA has determined that the stewardship program must include the following measures (also to be included as terms on the registration) that would minimize the potential for off-target movement and avoid the development of weed resistance.

#### **a. Investigation**

EPA has determined that the registration must contain a term that requires DAS or its representative to investigate reports of non-performance as reported by users following required "scouting" (in accordance with labeling requirements). When investigating these reports, DAS or its representative would be required to conduct site visits.

#### **b. Reporting of the Incidence of Likely Herbicide Resistance**

EPA has determined that the registration must contain a term that requires DAS to use the Norsworthy criteria for determining likely herbicide resistance and inform EPA if likely resistance has been identified. This information must be submitted to the Agency on a

monthly basis.

**c. Remediation**

EPA has determined that the registration must contain a term that requires DAS to take immediate action to eradicate likely resistant weeds in the infested area as well as requiring DAS to collect material for further testing.

**d. Annual Reporting of Herbicide Resistance to EPA**

EPA has determined that the registration must contain a term that requires DAS to submit annual summary reports to EPA that include a summary of the number of instances of likely and confirmed weed resistance by weed species, crop, county and state. The annual reports must include summaries of the status of laboratory or greenhouse testing for resistance. The annual reports would also address the disposition of incidents of likely or confirmed resistance reported in previous years. These reports would not replace or supplement adverse effects reporting required under FIFRA 6(a)(2).

**e. Reporting of Likely Resistance to other Interested Parties**

EPA has determined that the registration must contain a term that requires DAS to inform growers and other stakeholders of likely and confirmed resistance to Enlist Duo™. The information will include details of weed species and crop. EPA understands that DAS already plans to provide this information through a devoted website.

**f. Reporting on the development of diagnostic tests**

EPA has determined that the registration must contain a term that requires that DAS would inform EPA of DAS's progress toward diagnostic testing for evaluating resistant weed species.

**g. Monitoring the use of Enlist Duo™ on Enlist™ Seed**

EPA believes it is important to require DAS to monitor whether Enlist Duo™ is being used on the Enlist™ seed purchased from DAS. EPA has determined that the registration must contain a term that requires DAS to provide EPA with a protocol to survey whether Enlist Duo™ is being used on Enlist™ seed purchased from DAS and not the non-choline 2,4-D products that are not registered for these application windows. EPA expects that a protocol would be agreed upon quickly so that monitoring the use of Enlist Duo™ can begin shortly thereafter.

**h. Training and Education**

EPA has determined that the registration must contain a term that requires DAS to provide training on the use of Enlist Duo™ when it provides training on the Enlist™ Seed technology. The training would focus on proper use of the technology to avoid off-target movement as well as avoid weed resistance.

## **2. EPA's Continued Control over the Registration**

Because the issue of weed resistance is an extremely important issue to keep under control and can be very fast moving, EPA has determined that the registration must contain terms that ensure that EPA retains control to easily and quickly modify or cancel the registration if necessary.

## **3. Geographic Limitation on Use of Enlist Duo™**

EPA has determined that Enlist Duo™ would be allowed to be sold and used only for those states for which an endangered species assessment has been completed and resulted in a “no effect” determination. Currently, the states of Illinois, Indiana, Iowa, Ohio, South Dakota, and Wisconsin have been found to comply with these criteria. Additional states may be added to the labeling if assessments for those states are completed and demonstrate that a “no effects” determination is appropriate.